Dates and Times

Wednesday, September 24, 1997

4:00-6:00 PM **REGISTRATION**

Thursday, September 25, 1997

7:30-8:30 AM **REGISTRATION**

Session I

8:30-9:00 AM **INTRODUCTION**

Industry Perspective – High Level Overview
Krishan K. Arora, PhD
Electronic Regulatory Submissions,
Drug Regulatory Affairs
Novartis Pharmaceutical Corporation

CDER Perspective – High Level Overview
David C. Isom
CDER
Office of Information Technology
U. S. Food and Drug Administration

Session II

9:00-9:30 AM **GUIDANCE DOCUMENT**

Organization of The Guidance Document
David C. Isom
CDER
Office of Information Technology
U. S. Food and Drug Administration

Session III

9:30-10:00 **FILE FORMATS FOR ARCHIVING SUBMISSIONS**

PDF for Document Format
Gregory Brolund
CDER
Office of Information Technology
U.S. Food and Drug Administration

10:00-10:30 **REFRESHMENT BREAK**

Session IV

10:30 AM-12:00 PM **ARCHIVE SUBMISSIONS – NDA SUB SECTIONS**

Subsection 1.1 Table of Contents
Subsection 1.12 Case Report Forms
Randy Levin, MD
CDER/ODE
Division of Neuropharmacologic
Drug Products
U. S. Food and Drug Administration

12:00-1:00 PM **LUNCHEON**

Session IV: Continued

1:00-2:30 PM **ARCHIVE SUBMISSIONS – NDA SUB SECTIONS**

Subsection 1.11 Case Report Tabulations
Randy Levin, MD
CDER/ODE
Division of Neuropharmacologic
Drug Products
U. S. Food and Drug Administration

Session V

2:30-3:00 PM **SUBMITTING ARCHIVAL FILES**

Receiving the Archive Submission at CDER:
Expectations and Process
Gregory Warzala
CDER/OIT
Data Management Services
U. S. Food and Drug Administration

3:00-3:30 **REFRESHMENT BREAK**

Session VI

3:30-4:30 PM **PANEL QUESTIONS AND ANSWERS**

Panelists:
Krishan K. Arora, PhD, Novartis
Pharmaceutical Corporation
Michael Buster, FDA
Gregory Brolund, FDA
Kenneth Edmunds, FDA
David C. Isom, FDA
Randy Levin, MD, FDA
Gregory Warzala, FDA
Barry Wheeler, FDA

5:00 **WORKSHOP ADJOURNED**

Regulatory Submissions in E. Format: Industry Perspective - An Overview

Krishan K. Arora, PhD.

Electronic Regulatory Submissions, DRA

Novartis Pharmaceuticals Corporation

Bethesda, MD; September 25, 1997

NOVARTIS

INDUSTRY CONNECTION

- PhRMA (Pharmaceutical Research and Manufacturers of America)
- RACC (Regulatory Affairs Coordination Committee)
  - 16 companies
  - L. Versteegh, PhD, P&G, Chairs
- ERS - WG (Electronic Regulatory Submissions Working Group)
  - 12 companies plus FDA
  - ICH perspective
  - K. Arora, PhD, Novartis, Chair
  - R. Hizer, Lilly, Co-chair

OBJECTIVES

- Minimize Preparation Time and Cost of Submissions
  - Size of each submission
  - Uniformity of submission content and format across drugs and across agencies
- Expedite Agency Review and Decisions
  - Facilitate information access
  - Facilitate writing of assessment reports

WHY?

- IN the Year 1996 Alone
  - FDA spent $5M to manage 7.5 miles of paper applications
  - Industry spent $0.5-1.0M, plus 5-6 weeks, per NDA paper application (= $25-50M)
- Paperless Electronic Submissions Make Sense Although Industry Produces Paper Efficiently

HOW TO!

- Eliminate Redundant Data/Documents
  - Clinical data or CRTs; why both?
  - PDF or WORD/WP; why both?
- Replace Paper with Electronic Version
  - Paperless Submissions by the Year 2002
- Determine and Implement E. “Standards”
- Develop and Release “Guidance”
- Maintain a Global Perspective (ICH)

Electronic Standards

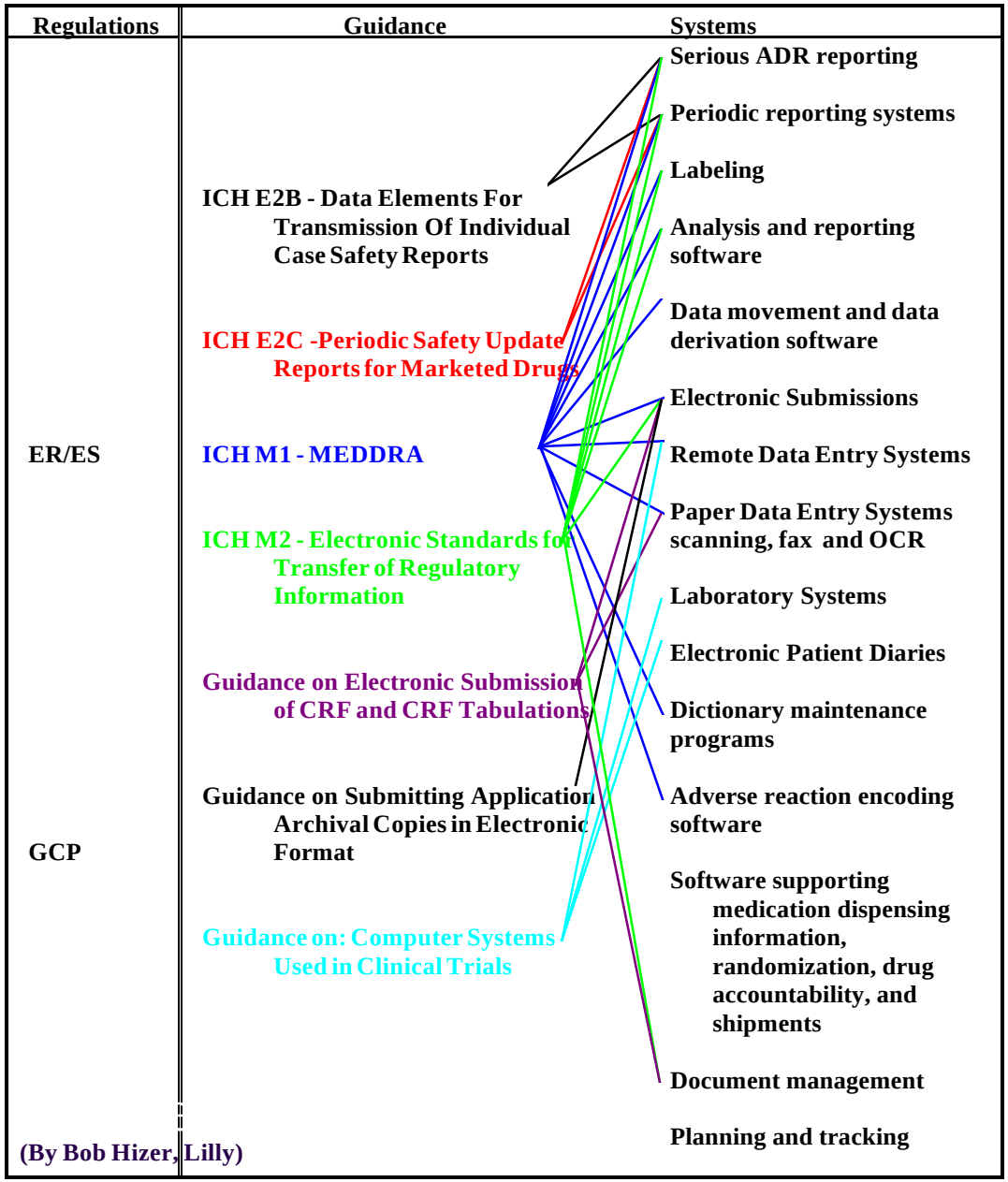
- Non-proprietary standards
  - lead to lowest denominator problems
- Proprietary standards
  - lead to version control problems
- Technology Watch
  - Leading edge technologies
  - Lagging edge technologies

CHALLENGES: Information Technology Industry

- Case Report Forms (CRFs)
  - Speed of scanning and bookmarking
  - Conversion from TIFF to PDF
  - Keyword search in PDF documents
- Case Report Tabulations (CRTs)
  - Patient level bookmarking very slow
  - Big file a problem from SAS to ASCII to WP
- PDF to WORD/WP Text for Cut-and-Paste
- Problem of Comparing PDF Documents

CHALLENGES: Pharmaceutical Industry (+CROs)

- Must Insist on Global Perspective
- Implementation of Standards and Guidance
  - Complex, requires large investment, long time
- Necessary and “Right” Thing To Do
- Each S/G Effects Multiple Systems
- Each System Effected by Multiple G/S


Regulations
Guidance
Systems
ER/ES
GCP
ICH E2B - Data Elements For Transmission Of Individual Case Safety Reports
ICH E2C -Periodic Safety Update Reports for Marketed Drugs
ICH M1 - MEDDRA
ICH M2 - Electronic Standards for Transfer of Regulatory Information
Guidance on Electronic Submission of CRF and CRF Tabulations
Guidance on Submitting Application Archival Copies in Electronic Format
Guidance on: Computer Systems Used in Clinical Trials
Serious ADR reporting
Periodic reporting systems
Labeling
Analysis and reporting software
Data movement and data derivation software
Electronic Submissions
Remote Data Entry Systems
Paper Data Entry Systems scanning, fax and OCR
Laboratory Systems
Electronic Patient Diaries
Dictionary maintenance programs
Adverse reaction encoding software
Software supporting medication dispensing information, randomization, drug accountability, and shipments
Document management
Planning and tracking
(By Bob Hizer, Lilly)

CHALLENGES: Regulatory Agencies

- Accommodate Global Viewpoint
- Come to the Electronic Age
- FDA CDER Leads:
  - Electronic CRFs/CRTs Without Paper
  - Plans for Entire NDA Without Paper
  - Coordination of Divisions within CDER
  - Coordination with CBER

CONCLUSIONS

- Excellent ROI on E. CRFs and CRTs
- What to addressed next?
- Cooperation among FDA, Industry and Vendors is essential
- Must keep in mind the COST factor
- All parties must maintain Global perspective

Regulatory Submissions in Electronic Format:
Industry Perspective - An Overview

(Krishan k. Arora, PhD, Novartis Pharmaceuticals Corporation, September 25, 1997)

It is indeed my pleasure to welcome you all at this unique conference, rather a unique workshop. I say it is unique because it is addressing a key regulation, a key time and resource consuming function - both for the FDA and for the pharmaceutical industry, a key activity that has the potential to revolutionize new drug development in the USA, and a key opportunity for Information Technology industry for innovation, entrepreneurship and business development. It is unique also because here we have under one roof a regulatory agency - the FDA, a pharmaceutical trade association - the PhRMA, and a professional association - the DIA, all three non-profit organizations cooperating to disseminate crucial information - how best to use guidance for electronic submissions of two sections of an NDA. This is only the first step towards many more to come until all sections of an NDA are possible electronically. Because, this is a workshop, attendance had to be kept limited, and you are among the lucky 200, or should I say the smart ones, to have registered early and got in. Many at the FDA have worked very hard to get the guidance document released in time for the Workshop. We appreciate their efforts especially the speakers for they had to work even harder. I believe, it will be a productive day, for industry to get many questions answered and for the FDA to receive solid feedback. So, without taking any more time, let me get on with my short presentation and give you an overview of the pharmaceutical industry perspective.

Industry Connection

Pharmaceutical Research and Manufacturers of America (PhRMA) has an active committee called Regulatory Affairs Coordination Committee (RACC) which oversees regulatory aspects of our business in USA and also collaborates with other agencies. About 16 pharmaceutical and biotech companies are members of RACC. Dr. L. Versteegh of Procter & Gamble chairs the committee. Under RACC is an Electronic Regulatory Submissions working group (ERS WG) which oversees the IT aspects of our business. It has about members from about 12 PhRMA companies and FDA. The group is active in supporting ICH-M2 (electronic transfer standards) and collaborates on several joint PhRMA-FDA information technology projects. Bob Hizer of Lilly and I co-chair ERS and are active members of ICH-M2.

Industry Objectives

Among the many objectives of the Pharmaceutical Industry here are a few that are relevant to this guidance, some are actually in line with FDA objectives. We want to minimize the time and resources required to prepare a submission. We believe this can be achieved by reducing the size of an application. Also, by making the content and format of submissions uniform from NDA to NDA and for agency to agency worldwide. After all, we are a global industry. The other equally important objective is to expedite the agency review and decision actions. We recognize this requires facilitating access to information in an application and also writing of the summary basis of approval or the assessment report, which in turn calls for special features such as browsing, cut-and-paste etc.

Why Paperless Submissions?

Why! Last year alone FDA spent almost 5 million dollars to manage 7.5 miles of paper applications. In addition, the industry spent on average, 0.5 - 1.0 million dollars and 5-6

weeks time per NDA of paper application. 7.5 miles of paper is a lot of trees, folks. Although, many in our industry have become rather efficient in producing paper submissions, paperless electronic submissions still make the most sense. But not, if it will cost more or take more time to prepare, or to review at the agency.

How To!

How do we go about achieving this! First, why not eliminate redundant data and/or documents? For example, if we are providing all clinical data electronically, why to provide CRTs - or voice-versa? Similarly, if we are providing reports in PDF format, can we not do away with Word or WordPerfect format? If electronic versions of reports are provided, why ask for paper copy as well? We support CDER director Dr. Janet Woodcock's goal of paperless submissions by the year 2002, even though some of us may not be fully ready by then. We welcome electronic standards, we welcome guidance - such as the guidance of today, but we also urge that the global perspective be maintained, because none of us, not even the number one company Novartis, which I work for, wants to or can afford to file different formats of the same submission in different countries. Hopefully, the ICH Common Technical Document expert working Group will resolve the content and the format differences among regions.

Electronic Standards

As an active member of the ICH-M2 expert working group on electronic standards, I have witnessed spending endless hours searching non-proprietary standards and debating their practical merits and demerits. Whereas, agency representatives find themselves caught not to favor one proprietary solution over another, the industry representatives find proprietary solutions often more palatable - with some assurances of course, such as viability of vendors and version control of software etc. No matter what standard are adopted, there will always be a need to switch to leading edge technology solutions as they become available; and there will always be a need to continue support of lagging edge technology solutions in order to keep the small companies afloat, or where and when a leading edge solution may not be cost effective anymore more.

Challenges for IT Industry

That leaves us with some very specific challenges for all three parties. IT industry needs to find solutions for FAST, I repeat FAST, scanning of CRFs and fast creation of bookmarks. Many CRF images are in TIFF, their conversion to PDF- FAST and inexpensive conversion - is still a challenge. Searching CRFs in PDF by key words still begs for an easy solution. Similarly, creating bookmarks in a large CRT table, by say patient ID, is slow; converting SAS output of a large CRT to ASCII and/or to WP for printing has been a big headache. Printing jobs for large listings or tables abort more often than not. Cut-and-paste from PDF to Word or WP for editing is slow and cumbersome for text, and worst for tables, even with use of popular plug-ins. There is just no practical way for one to compare electronically two versions of a PDF document, whereas it is a piece of cake for Word or WP versions.

Challenges for Pharmaceutical Industry

For pharmaceutical industry, it is not a happy challenge to deal with - with so many regional preferences. Converting same report into PDF for US, into HTML for SEDAMM in France, into DAMOS for Germany, into SGML for MERS in Canada etc., are just too many to deal with. Implementation of various standards and guidance requires considerable amount of time

and a sizable investments in IT, for SOPs, and for personnel. Never-the-less, it is the right thing to do and the pay back could be worthwhile.

As you can see from the next slide, each standard or guidance affects many systems and every system is affected by many standards and guidance.

Shear management of modifications to these systems could cost arm and length. The impact of "FDA 21 CFR Part 11 electronic ; electronic record; the final rule" to make all GxP systems maintain computerized audit trails could cost millions of dollars; this is no exaggeration.

Challenges for the FDA

Challenges for FDA are just as difficult but also is the "right thing to do". I think, I have already emphasized enough the global viewpoint, which is just as important for the FDA. I am also pleased to note that the CDER director Dr. Woodcock fully agrees with the global aspects and the message is tickling down in her organization. FDA must continue to enhance the IT environments. CDER is leading the way with electronic CRFs and CRTs which is to follow with other sections. This must happen in all divisions and in CBER.

Conclusions

Return on investment of electronic CRFs and CRTs is good. At Novartis, we have found their cost to be considerably less than submitting paper, even when we paid an outside vendor company to create electronic. CRFs and CRTs. The obvious question is what other sections of NDA should be next? We encourage you to help prioritize additional sections where you think the impact will be high. Cooperation between FDA, pharm and IT industry, and I don't mean to leave out CROs, is important, although we still need to keep certain distance between us because of the potential conflict of interest. Cost factor is very important for all three parties, and it is the best incentive for CEOs. And, once again, let us maintain the global perspective. Thank you.

DIA Workshop
GUIDANCE FOR INDUSTRY: Regulatory Submissions in Electronic Format

David Isom
Acting Director, Office of Information Technology
Center for Drug Evaluation and Research
September 25, 1997

Session I: Introduction

- CDER IT Focus
  - Capability for electronic regulatory submission and review by 2002
- Areas of concentration
  - Focused IT supporting cast and planning
  - **e-collection, submission, and archive (Today's topic: submission and archive)**
  - e-review and resources
  - e-document management system
  - e- access for the public (web)

Electronic Submission

- You can submit regulatory submissions in electronic format in lieu of paper provided:
  - regulations (21 CFR part 11) are met, and
  - document type is identified in the Agency's public docket (no. 92S-251)
- Guidance for CDER's first document types
  - CRF/CRTs subsections of the New Drug Application (NDA)
  - This will replace CDER's waiver policy

Background: CRT/CRF subsections

- CRT/CRF and Archiving Groups formed
- Draft Guidances introduced at a Nov 96 DIA
- Based on internal and external comments, we combined the Guidances to one
- Further stds and function work continues
- Today's CDER speakers are key contributors to this new guidance

Session II: Organization of the Guidance

- Introduction
- Organization of the guidance
- File formats for archiving
- Other file formats
- Organization and submission
- Specific submission (document) types
  - follows the 356h form

Introduction

- Voluntary to submit the document types we publish in the public docket
- Reduces the need to consult CDER on details that ensure your e-submissions can be handled, reviewed, and maintained
- The ‘Archiving Submissions in Electronic Format--NDAs’ is a first of a series.

File Formats for Archiving

- What CDER is prepared to archive and accept in lieu of paper regulatory copy
- PDF (portable document format)
- General information
  - reasons for selection
  - recommendations for fonts, page orientation, indexing, hypertext linking, etc.

Other File Formats (OFF)

- Any electronic format or functionality not covered in the archive guidance:
  - Needed because we can't do everything at once
  - Submit directly to the review division as you do in today's 'CANDA' model. However,
  - will not be acceptable to replace the paper
- The archive guidance will increase as we gain experience and as technology improves so we can decrease OFF submissions
- Our years of CANDAs and OFFs got us here

Submitting Archival Files

- Organization of the files and directories
- Where to submit the single copy
- Media we can manage
- How to label and bind the media
- Include a paper copy of the cover letter, 356h, and table of contents

Amendments

- Amendments to the specified document types will follow as soon as possible. However, the first priority is to complete all subsections of the initial application.

Subsections- follows the 356h form

- Contents
  - Each subsection provides regulatory references and recommendations for file organization, information fields, TOC, hypertext linking, and indexing recommendations
- Only item 1 (Index), item 11 (CRTs) and item 12 (CRFs) will be in the guidance to start
  - Only item 11 and 12 are initially in the docket
- Several other subsections are already in draft
- Data? Coming, but have more work to do

Technical Support and Questions

- Mr. Ken Edmunds, OIT Electronic Submissions Coordinator, email ESUB@CDER.fda.gov

Using PDF for Electronic Submissions

Greg Brolund
CDER / FDA
September 25, 1997

Overview

- Why PDF for text
- General PDF recommendations

Why PDF ?

- Archivable
- De facto standard
- Recommended ICH standard for text submission
- Possible ISO Standard

PDF Advantages

- Relatively low cost yet functional in terms of implementation and support.
- Free viewer
- Creation using a PDF device driver or from any Postscript file
- Detailed advance technical agreements are not necessary (as in SGML DTD)

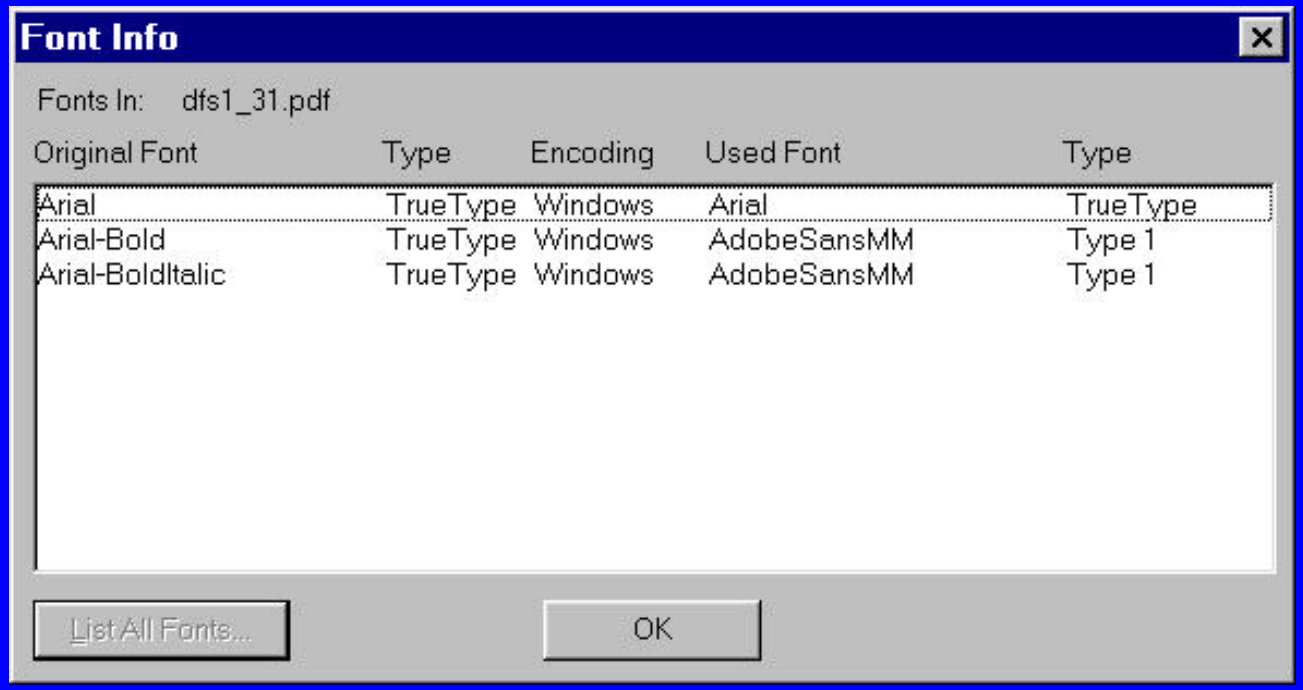
PDF Advantages

- Functional navigational aids
- International support
- Multiple source (Word processor, HTML, SGML and TIFF)

General PDF Recommendations

Fonts

- Limit # and embed in document

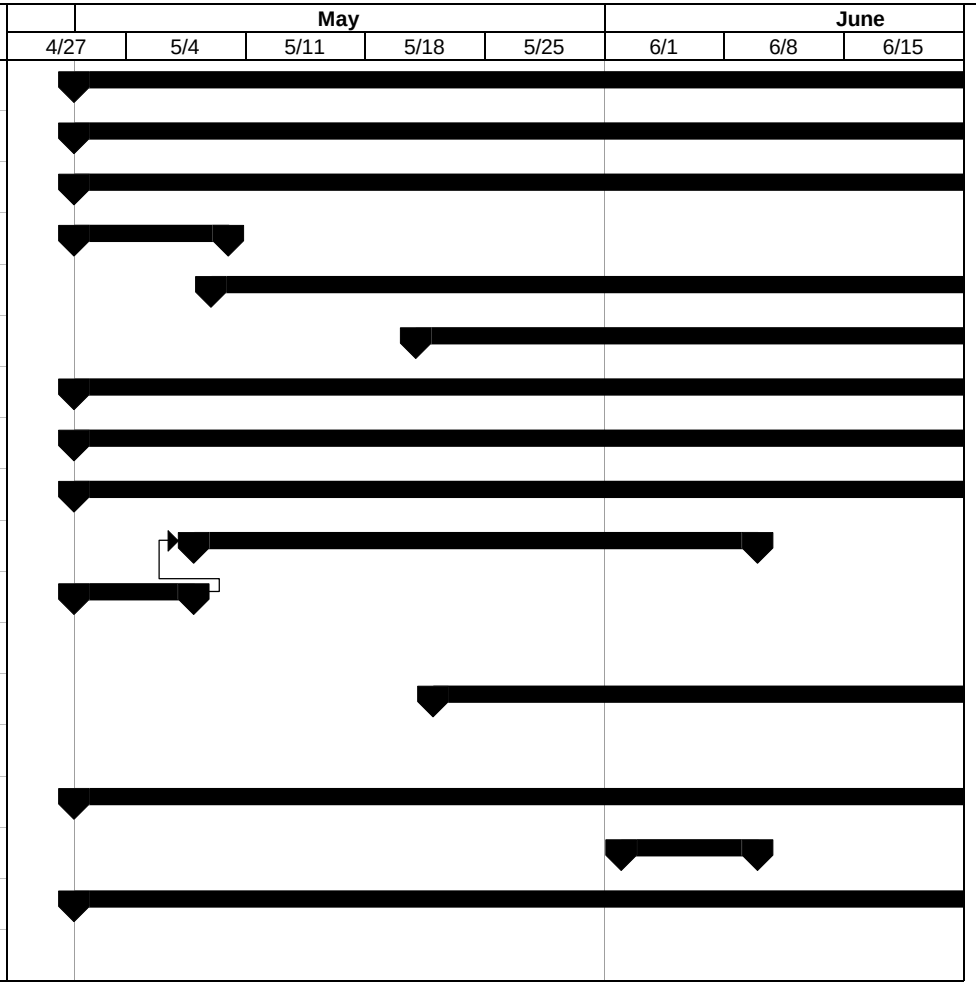


Page Orientation

- Present correct orientation

DFS 1.3 Schedule

ID	Task Name	Duration	Start	Finish
1	**Deliver Phase 1.3**	99d	5/1/97	9/17/97
2	***Code Enhancements***	87d	5/1/97	8/29/97
3	**Develop Application Standards -V**	74d	5/1/97	8/12/97
6	**Customization**	7d	5/1/97	5/9/97
13	**Search**	63d	5/9/97	8/5/97
19	**Attributes**	61d	5/21/97	8/13/97
26	**Bring into DFS**	63d	5/1/97	7/28/97
37	**Sign Off**	76d	5/1/97	8/14/97
48	**Routing**	77d	5/1/97	8/15/97
56	**Autorender**	23d	5/8/97	6/9/97
64	***Set up Configuration Management***	5d	5/1/97	5/7/97
68	***Install Target***	3d	7/25/97	7/29/97
72	***Develop Test Plan***	62d	5/22/97	8/15/97
77	***Integration Testing***	12d	9/2/97	9/17/97
83	***Training Preparation***	86d	5/1/97	8/29/97
90	***Configure Training Room***	6d	6/2/97	6/9/97
96	***Deliver User Guides***	95d	5/1/97	9/11/97
103	***Deploy Phase 1.3 to Pulmonary***	47d	8/4/97	10/8/97



DFS 1.3 Schedule

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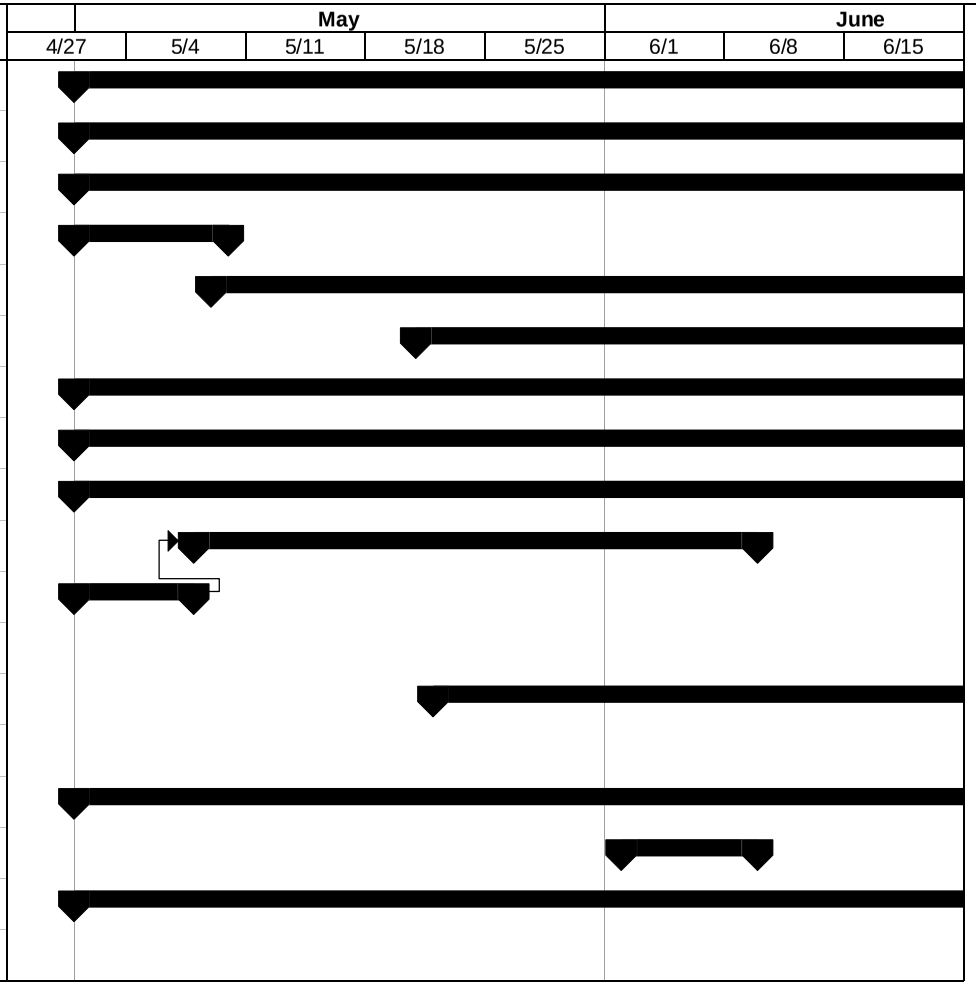
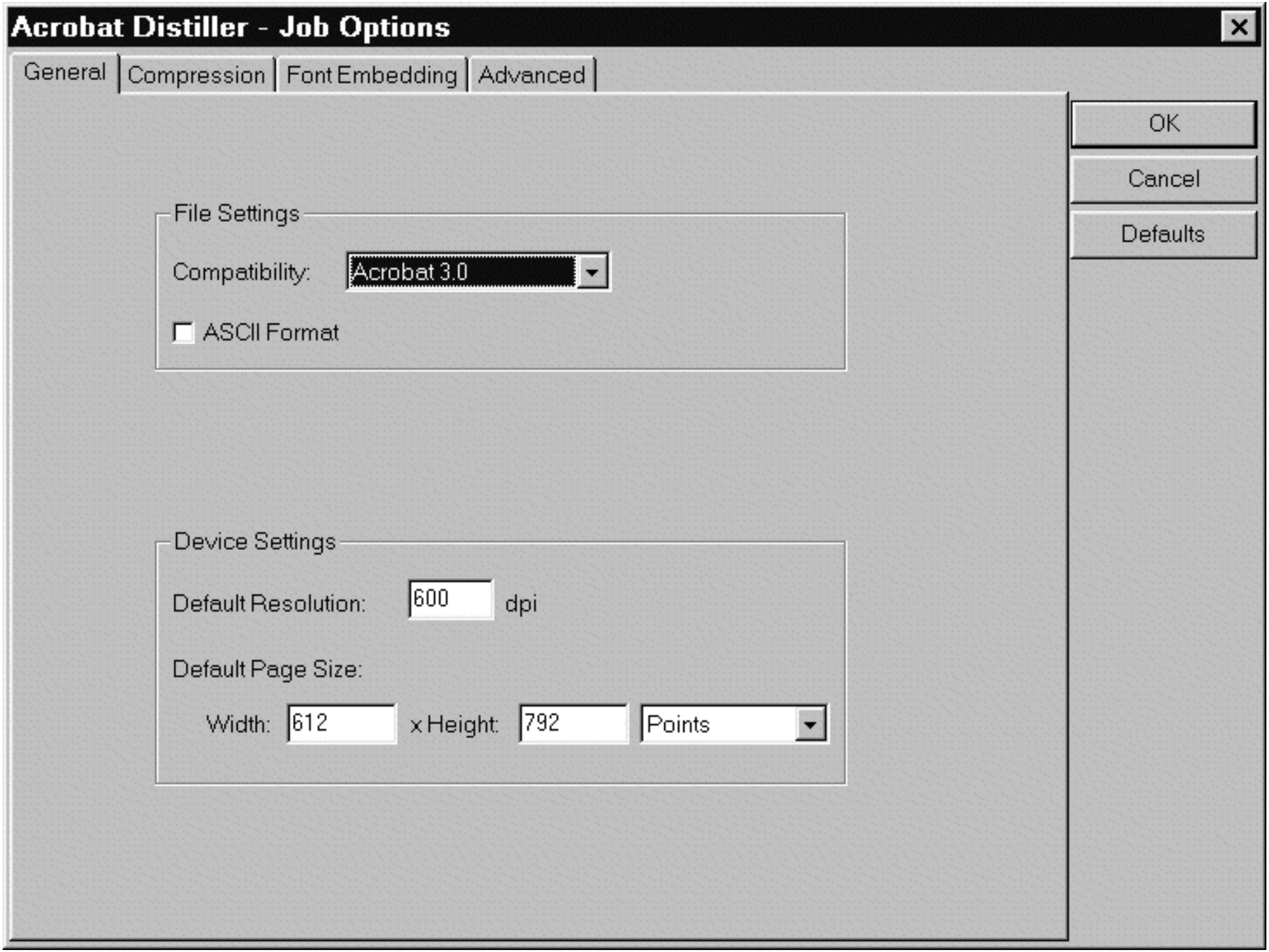
3	Develop Application Standards -V	74d	5/1/97	8/12/97
6	Customization	7d	5/1/97	5/9/97
13	Search	63d	5/9/97	8/5/97
19	Attributes	61d	5/21/97	8/13/97
26	Bring into DFS	63d	5/1/97	7/28/97
37	Sign Off	76d	5/1/97	8/14/97
48	Routing	77d	5/1/97	8/15/97
56	Autorender	23d	5/8/97	6/9/97
64	*Set up Configuration Management*	5d	5/1/97	5/7/97
68	*Install Target*	3d	7/25/97	7/29/97
72	*Develop Test Plan*	62d	5/22/97	8/15/97
77	*Integration Testing*	12d	9/2/97	9/17/97
83	*Training Preparation*	86d	5/1/97	8/29/97
90	*Configure Training Room*	6d	6/2/97	6/9/97
96	*Deliver User Guides*	95d	5/1/97	9/11/97
103	*Deploy Phase 1.3 to Pulmonary*	47d	8/4/97	10/8/97



Original Documents

- Use electronic document as the source whenever possible
- Acrobat Distiller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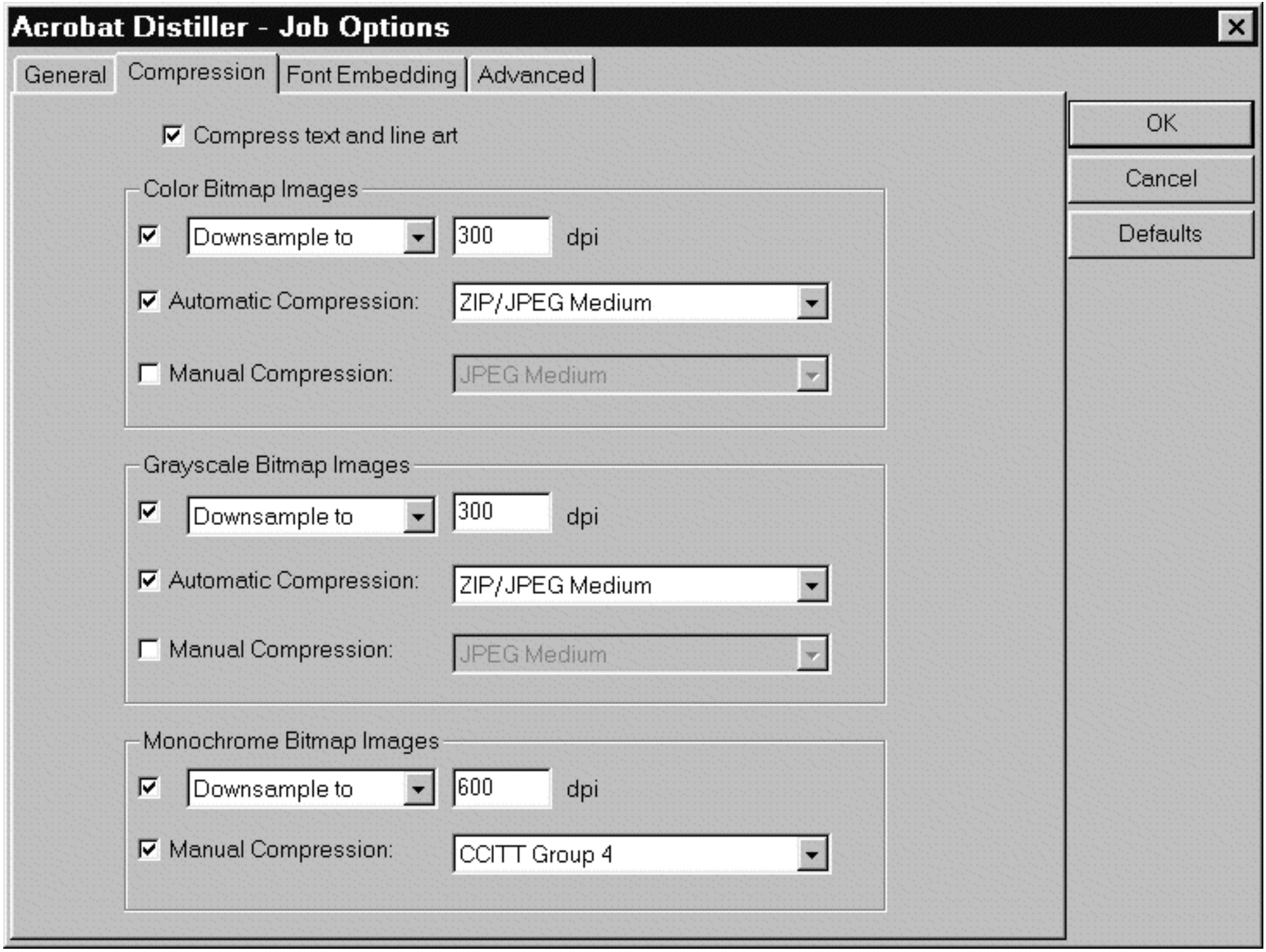
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Manual Compression:
JPEG Medium
Grayscale Bitmap Images
Downsample to
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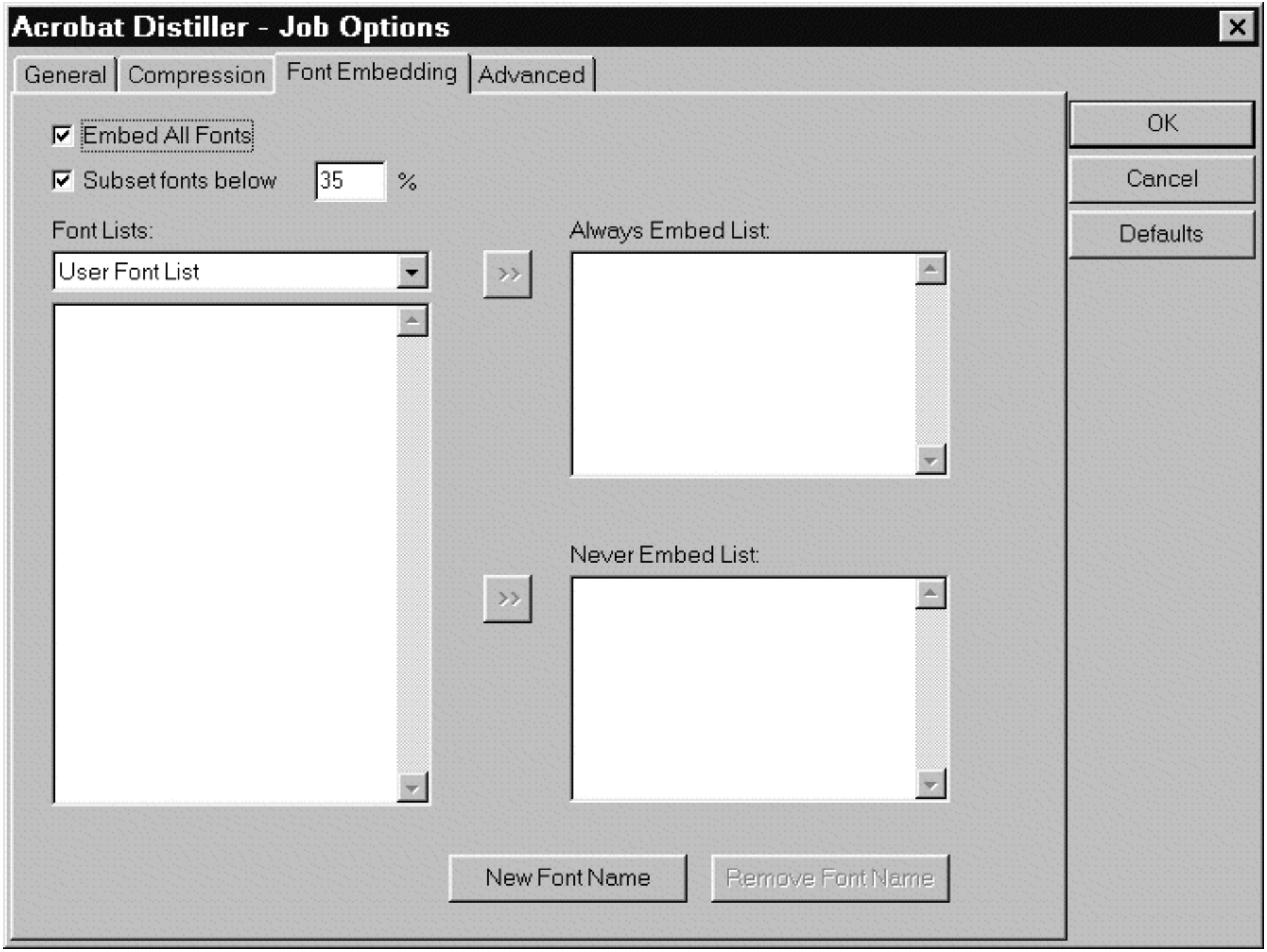
CCITT Group 4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New Font Name
Remove Font Name
OK
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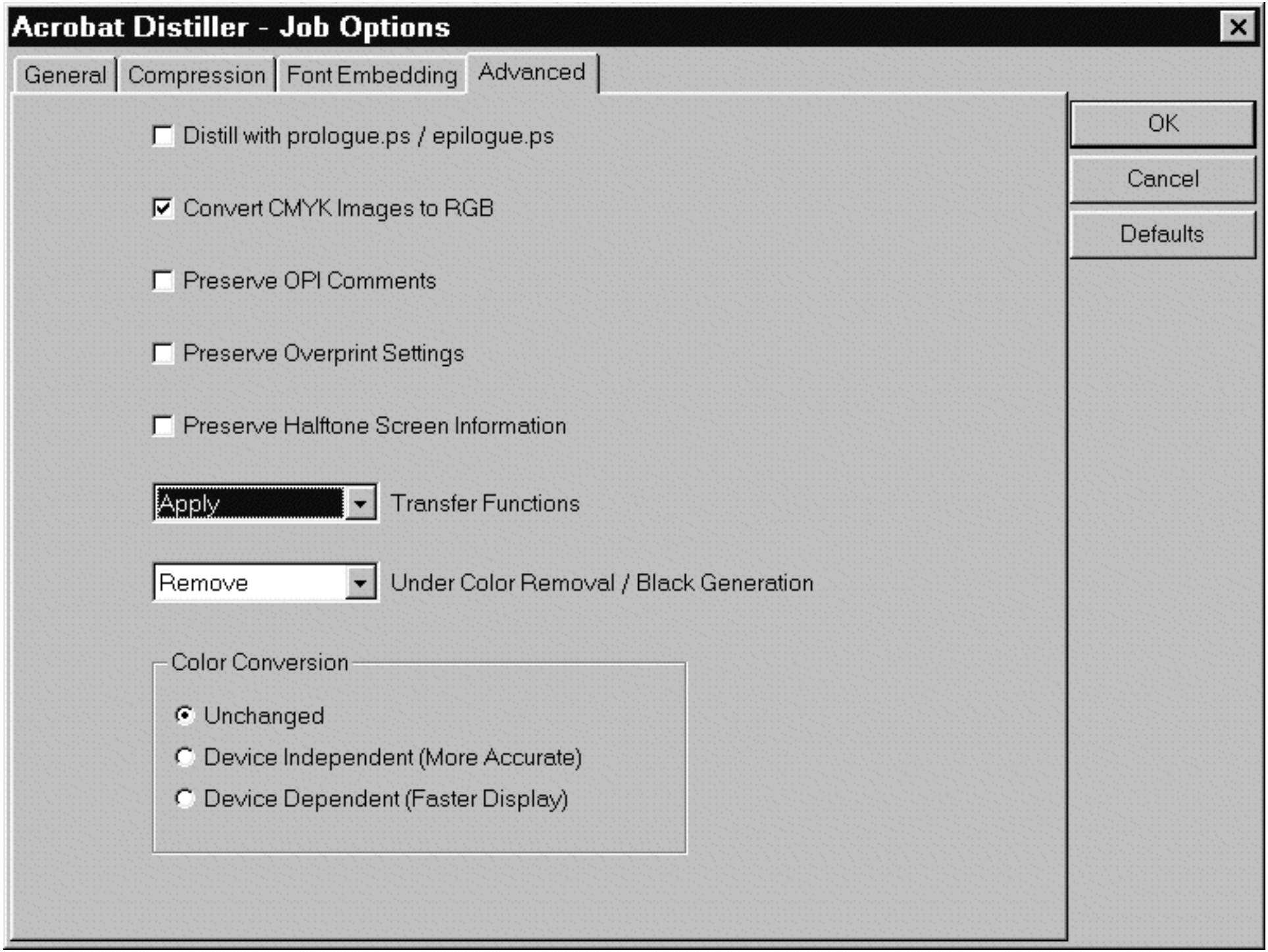
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Distill with prologue.ps / epilogue.ps
Convert CMYK Images to RGB
Preserve OPI Comments
Preserve Overprint Settings
Preserve Halftone Screen Information
Apply
Transfer Functions
Remove
Under Color Removal / Black Generation
Color Conversion
Unchanged
Device Independent (More Accurate)
Device Dependent (Faster Display)
OK
Cancel
Defaults

Paper Documents

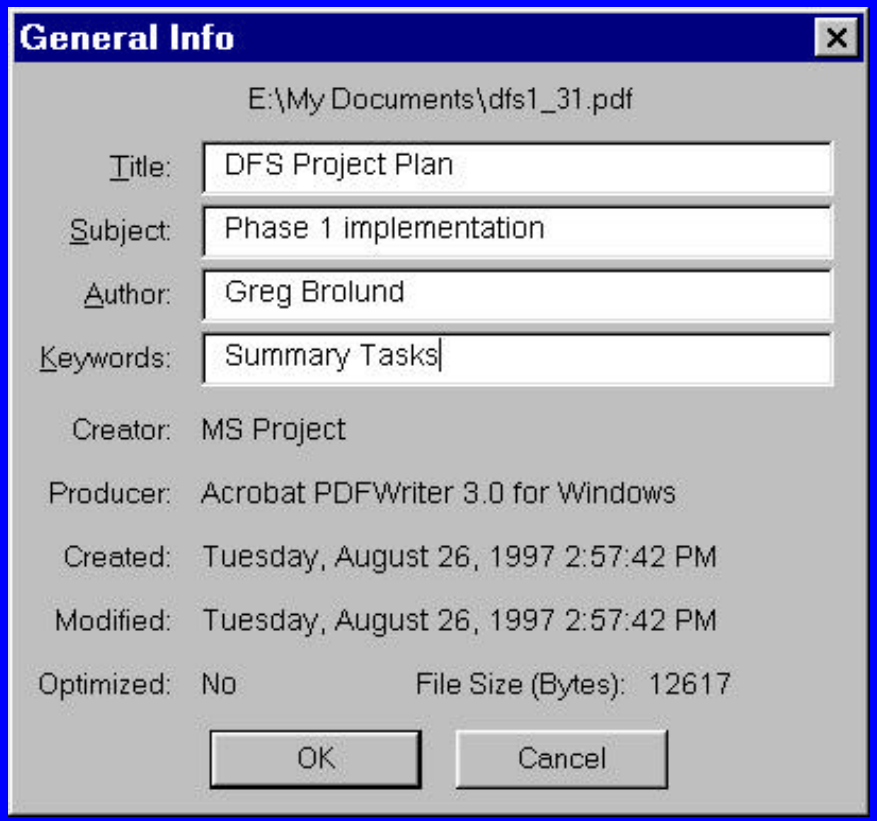
- Select appropriate scanning resolution
- Black and white, if possible, to minimize size
- 8 bit gray scale or 24 bit RGB if necessary

Hypertext and Bookmarks

- Use as necessary
- See specific subsections for recommendations

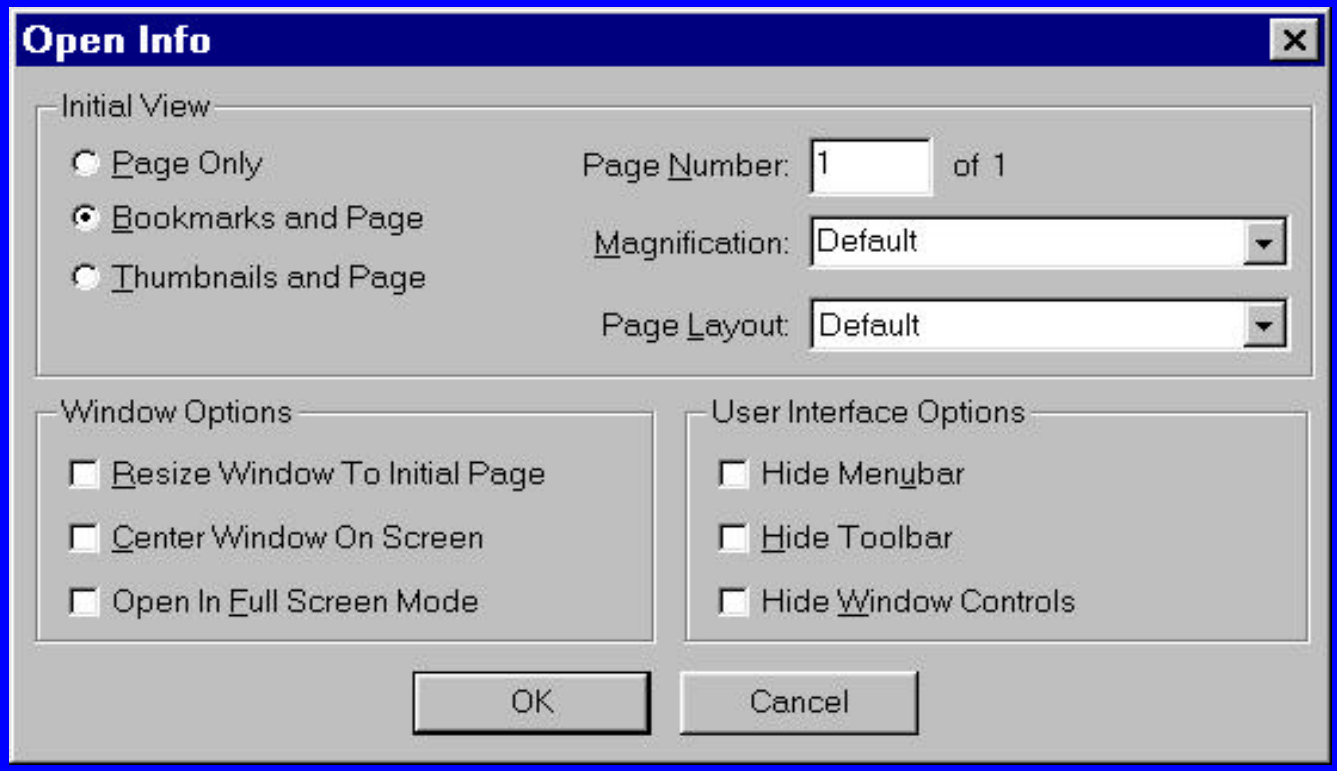
Document Information Fields

- Searchable, see subsections



Open Dialog Box

- Initial view -> Bookmarks & Page
- Magnification and Page Layout to default

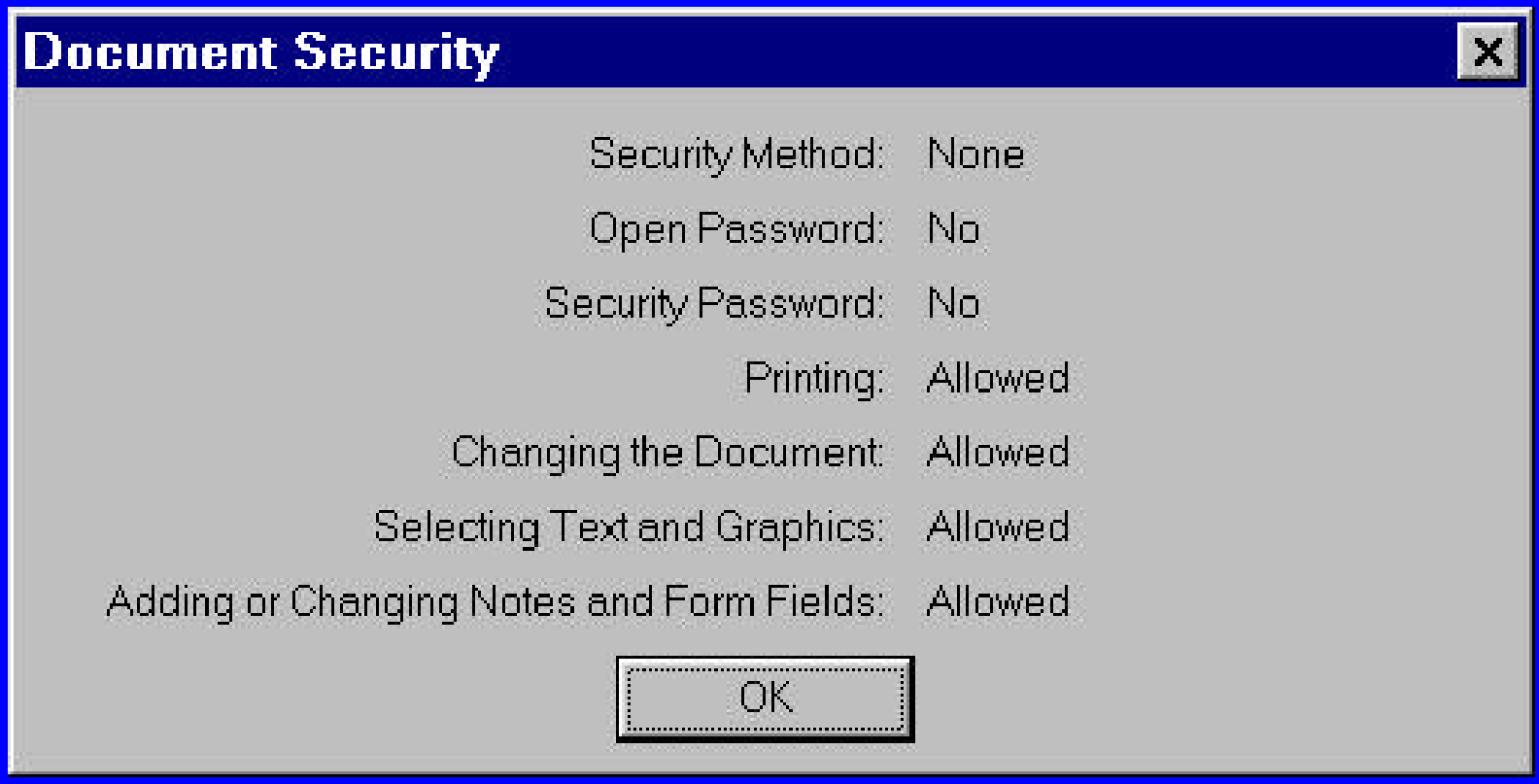


Naming PDF Files

- No long file names at this time
- report12.PDF
- See specific subsections for additional naming recommendations

Security

- Do not restrict access



Indexing

- Acrobat Catalog
- Subdirectory for indexes
- See subsections for additional recommendations

U.S. Food and Drug Administration
Center for Drug Evaluation and Research

Submitting Archival Files

To the CDER

Electronic Document Room

Greg Warzala

Director, Division of Data Management & Services

September 25, 1997

Submitting Archive Files

Electronic
Document
Room

- ***The Guidance has been written to make all our lives easier . . .***

Greg Warzala
Division of Data Management and Services

Submitting Archive Files

- ***We Want to Outline***
  - ***Sponsors' Part***
  - ***Our Part***

To make things go smoothly

Submitting Archive Files The Sponsor's Part . . .

Electronic
Document
Room

- ***Preparing the materials*** -
  - *file organization &*
  - *file names are*

Critical to a successful mount

Submitting Archive Files The Sponsor's Part . . .

Electronic
Document
Room

- ***Acceptable Media***
  - *3.5 inch diskettes (10)*
  - *ISO 9660 CD-ROMs (5)*
  - *DLT 20/40 or 10/20 GB tape*

    Backups created using

    OPENVMS or Windows NT

Submitting Archive Files The Sponsor's Part . . .

Electronic Document Room

- ***Physical Preparation***
  - ***Place in a standard binder***
  - ***Label Binder & Disks***
  - ***Include cover letter***
  - ***Helpful: descriptive info***

Submitting Archive Files
The Sponsor's Part . . .

Electronic
Document
Room

- ***All Electronic Submissions***

  (Including Amendments & Supplements)

  Send to:

  CDER Central Document Room
  12229 Wilkins Ave.
  Rockville, Md. 20852

Submitting Archive Files
The EDR Staff Will . . .

Electronic
Document
Room

- ***Complete Standard Processing***
  - –Bar Code and Scan
  - –Separate Electronic & Paper
  - –Move to the EDR

Submitting Archive Files
The EDR Staff Will . . .

Electronic
Document
Room

- ***Begin Electronic Processing***
  - ***Initial Inspection***
  - ***Upload to VMS Server***

Submitting Archive Files
The EDR Staff Will . . .

Electronic
Document
Room

- ***Check for Conformance***
  - ***Information Presentation***
  - ***Links & Navigation***
  - ***Indexing***

Submitting Archive Files
The EDR Staff Will . . .

Electronic
Document
Room

- ***Create Archival Tapes***
  - ***Transfer to Appropriate Network Location***
  - ***Enter Location into Database***
  - ***Notify SCSO, CSO, Division Document Rooms***

Submitting Archival Files
The EDR Staff Will . . .

Electronic
Document
Room

- ***Two Archival Tapes***
  - ***One Stored at CDR***
  - ***One Copied to Network and Incorporated into Backup Routines***

Submitting Archive Files
The EDR Staff Will . . .

Electronic
Document
Room

- ***Problem Resolution*** **-**
  - ***Complete logs & technical data***
  - ***Recommendations***

SCSO will contact sponsors

Submitting Archive Files